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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,757	02/08/2001	Yechezkel Barenholz	BARENHOLZ=1	6619

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,757	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19-33* is/are allowed.

6)☒ Claim(s) *34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detection of probes which comprise the pH or potential sensitive fluorophore attached to a steroid, to a head group of a sphingolipid or to the head group of a lipid have two 14 carbon chains which probes interact with a lipid bilayer, does not reasonably provide enablement for any pH- or potential sensitive fluorophore without other structural information which interacts with any surface whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detection of binding of a species by detecting a fluorophore probe which interacts with the surface. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of determination of the binding of a species to a surface, but the surface is not delimited in the claims and for claims 34 and 35, the fluorophore probe is not structurally delimited either. The claims read on any surface, whether the lipid bilayer shown in the specification or an air/water interface or into a polymer or into the surface of a piece of wood. Further, claims 34 and 35 read on any probe with any structure whatsoever, so long as it encompasses a fluorescent probe.

Quantity of Experimenation

The quantity of experimentation in this area is extremely large since there is significant variability in the ability of compounds to be incorporated into surfaces. It would require significant and inventive experimentation to determine which groups, if any, could be attached to the fluorophore to stably incorporate the group at the surface of an air/water interface, the surface of a polymer, or the surface of a other compounds not specifically discussed or treated in the specification. Further, even with regard to the narrower embodiment of lipid bilayers, it would require significant experimentation to identify other stabilizing agents which could function other than those expressly listed in claim 19.

The unpredictability of the art and the state of the prior art

The prior art of Zuidam teaches that the fluorophore can be incorporated into a membrane but the short carbon chain linked to the fluorophore was unable to stably interact with the surface. Thus, the broad nature of claim 34 is not supported by the prior art which suggests that it is unpredictable what elements are necessary for function in the species detection method. Further, the prior art of Gee, while teaching fluorophores, makes no suggestion of stable incorporation at surfaces.

The use of flurophores on any surface for species detection is extremely unpredictable since it is unpredictable what effects the surface interactions will have on the fluorophore, it is unpredictable what elements are necessary to stabilize the fluorophore in a position near any surface and it is entirely unpredictable what elements of the fluorophore would function in a surface independent manner. For example, it is unpredictable what fluorophore would retain pH effect at an air/water interface, at an air/polymer interface or at an organic solvent/water interface. Even after identifying fluorophores, if any exist, which would function at these interfaces, the next step would be identifying components which would permit stable association of the fluorophores with the surfaces. This would require significant inventive chemical effort since each component would necessarily be specific for the fluorophore used and different fluorophores will have different chemical properties yielding different components necessary for stabilization.

Working Examples

The specification has a working example using hydroxycoumarin linked to dioleoyl phosphatidyl ethanolamine used in a lipid bilayer type surface, but there are no

working examples using surfaces other than lipid bilayers or other fluorophores besides hydroxycoumarin or components for stabilization other than dioleoyl phosphatidyl ethanolamine.

Guidance in the Specification.

The specification, while suggesting the use of lipid bilayers and fluorophores generally and certain lipid based components for stabilization, did not teach the use of any other surface besides lipid bilayers and did not teach fluorophores and components which would function in any surface other than lipid bilayers.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching against the use of any surface and any stabilization component by the art is opposed to patentability (see Zuidam and Gee). The specification provides one with no written description or guidance that leads one to a reliable method using any surface for detection. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a single narrow working example and the negative teachings in the prior art balanced only against the high skill level in

the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

Claims 34 and 35 encompass a genus of fluorophores whose fluorescence is dependent upon the binding or dissociation of a species at a surface. However, only three specific species of such fluorophores are even suggested by the specification, those linked to steroids, linked to sphingolipids or linked to lipids having at least two

chains of 14 atoms. The genus includes variants for which no written description is provided in the specification including essentially any other chemical modification whatsoever. Thus, applicant has express possession of only three particular species, in a genus which is almost literally infinite and which clearly comprises hundreds of millions of different possibilities. Here, no common structural element or attributes of the genus of binding insensitive fluorophores are disclosed.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the stable fluorophore lacks any specific structure and is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the three named species, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to any fluorophore for a method where one is "observing a change in a

fluorescent property ... upon binding or dissociation of a species" where the only change induced by the species is the change in pH or surface potential.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a stable fluorophore, without any definition of the particular structural components required to achieve this function.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any stable fluorophores other than those expressly disclosed which comprise the three species. Therefore, the claims fail to meet the written description requirement by encompassing compounds which are not described in the specification.

Allowable Subject Matter

3. Claims 19-33 are allowed.

4. The following is a statement of reasons for the indication of allowable subject matter: Claims 19-33 are now limited to lipid based surfaces. As noted previously, there is no prior art which teaches the method now claimed. Also, the issue of enablement is overcome by the limitation of the claim to a lipid based surface, as opposed to the use of any surface.

Response to Arguments

5. Applicant's arguments filed March 26, 2003 have been fully considered but they are not persuasive.

Applicant's amendment to claim 19 renders this claim and it's dependent claims allowable.

Applicant argues that the rejections of claims 34-36 is overcome because it is not unpredictable what elements are required. However, Applicant's entire argument, entire specification and entire support revolve around lipid bases surfaces as claimed in claim 19. Applicant has no teaching in the specification regarding any non-lipid based surface. All three of the working examples identified by Applicant are limited to lipid based surfaces and do not support a more generic claim. Even in Applicant's arguments, at page 11, the argument is that the claim is limited to lipid based surfaces. While this is correct and persuasive regarding claims 19-33, this is not correct regarding claims 34, 35 and 36. These claims have no limitation regarding the surface.

Consequently, Applicant's arguments based upon the limitation to lipid based surfaces does not apply to these claims.

With regard to the written description rejection, the deletion of the language regarding the fluorophore does not change the essential nature of the claim. In claims 34 and 35, no particular surface and no particular fluorophores are recited. More problematic is that no specific fluorophore structures which can achieve the observation goal are described other than the three species given. Consequently, the written description rejection is maintained because Applicant has not shown possession of other species which permit "observing a change in a fluorescent property ... upon binding or dissociation of a species" where the only change induced by the species is the change in pH or surface potential.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

May 15, 2003